Alicaforsen, an Antisense Inhibitor of Intercellular Adhesion Molecule-1, in the Treatment for Left-Sided Ulcerative Colitis and Ulcerative Proctitis

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Abstract: BACKGROUND Data on the efficacy of intercellular adhesion molecule-1 antisense oligonucleotide alicaforsen in ulcerative colitis (UC) is inconsistent. METHODS All patients, who had received at least one dose of alicaforsen, were analyzed retrospectively. Alicaforsen's efficacy was assessed in patients treated for left-sided UC and proctitis by comparing clinical and (if applicable) endoscopic disease activity before/after treatment. RESULTS Twelve patients were treated for left-sided UC or proctitis. Eleven patients received a 6-week course of a once-daily 240 mg alicaforsen enema formulation. In 1 patient, treatment was discontinued, because it was found to be inefficient. Disease activity measured by the partial Mayo score and 6-point symptom score was significantly reduced after treatment (6.0 vs. 2.4, p = 0.011 and 3.7 vs. 1.4, p = 0.008). Faecal calprotectin showed a trend towards reduction (484.4 vs. 179.5 g/g, p = 0.063). Clinical improvement was achieved in 10 patients (83.3%). In 7 patients, a relapse occurred (70%). Median duration of clinical improvement was 18.0 weeks (range 1-112). Three patients showed an ongoing improvement of >9 months. No adverse events were reported. CONCLUSIONS A 6-week course of alicaforsen seemed to be safe and efficacious in inducing clinical improvement in patients with left-sided UC and proctitis. Prolonged clinical improvement was observed in many but not all patients.

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Alicaforsen, an Antisense Inhibitor of Intercellular Adhesion Molecule-1, in the Treatment for Left-Sided Ulcerative Colitis and Ulcerative Proctitis

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Keywords
Alicaforsen · Antisense oligonucleotide · Left-sided ulcerative colitis · Ulcerative proctitis · Inflammatory bowel disease · Relapse

Abstract
Background: Data on the efficacy of intercellular adhesion molecule-1 antisense oligonucleotide alicaforsen in ulcerative colitis (UC) is inconsistent. ***Methods:*** All patients, who had received at least one dose of alicaforsen, were analyzed retrospectively. Alicaforsen's efficacy was assessed in patients treated for left-sided UC and proctitis by comparing clinical and (if applicable) endoscopic disease activity before/after treatment. ***Results:*** Twelve patients were treated for left-sided UC or proctitis. Eleven patients received a 6-week course of a once-daily 240 mg alicaforsen enema formulation. In 1 patient, treatment was discontinued, because it was found to be inefficient. Disease activity measured by the partial Mayo score and 6-point symptom score was significantly reduced after treatment (6.0 vs. 2.4, $p = 0.011$ and 3.7 vs. 1.4, $p = 0.008$). Faecal calprotectin showed a trend towards reduction (484.4 vs. 179.5 µg/g, $p = 0.063$). Clinical improvement was achieved in 10 patients (83.3%). In 7 patients, a relapse occurred (70%). Median duration of clinical improvement was 18.0 weeks (range 1–112). Three patients showed an ongoing improvement of >9 months. No adverse events were reported. ***Conclusions:*** A 6-week course of alicaforsen seemed to be safe and efficacious in inducing clinical improvement in patients with left-sided UC and proctitis. Prolonged clinical improvement was observed in many but not all patients.

Introduction

Gut-selective immunosuppressive agents, such as vedolizumab or mongersen, are very promising given their good efficacy, but have lower rates of side-effects compared to anti-tumor necrosis factor (TNF) treatment [1–3]. Infectious complications of anti-TNF remain a significant concern in clinical treatment decision and development of highly gut-selective therapies interacting with gut inflammation, but preserving systemic immune response has become a priority in the field of inflammatory

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bowel disease (IBD) research [4]. Such therapies take advantage of the specific molecular interactions in leukocyte trafficking [5]. Leukocyte trafficking is a multistep process involving both the immune and the endothelial cells, which enables direction of leukocytes to the site of inflammation: leukocytes tether, get activated, adhere to the endothelium and finally migrate through the endothelial layer. For this sequence, interaction between proteins on the surface of leukocytes and their corresponding ligands are crucial: integrins are expressed on immune cells and bind to their counterpart molecules of the immunoglobulin superfamily on endothelial cells. The latter consists of intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule or mucosal vascular addressin cell adhesion molecule. While mucosal vascular addressin cell adhesion molecule interacts with α4β7 integrin, which is therefore causative for the efficacy of vedolizumab, ICAM-1 is a transmembrane glycoprotein expressed on the surface of intestinal epithelial cells and vascular endothelial cells that binds to β2 integrins and therefore promotes firm adhesion of leukocytes to the endothelium [6, 7]. Expression of ICAM-1 is upregulated by TNFα, interleukin-1, interferon-γ and/or lipopolysaccharide [8]. Inflammation triggered by those factors (such as in IBD) results in an increased leukocyte adhesion and trafficking. Several studies suggest that an increased expression of ICAM-1 is a part of the pathology of IBD [9–14], which has led to the idea of blocking the ICAM-1 pathway in IBD treatment.

Alicaforsen is a human ICAM-1 antisense oligonucleotide, which blocks ICAM-1 production by complementary hybridization to the messenger ribonucleic acid of the target gene resulting in hydrolysis of the created deoxyribonucleic acid-ribonucleic acid (DNA-RNA) complex by an RNase enzyme [15]. While the systemic administration of alicaforsen in Crohn's disease (CD) was not efficacious [16–18] and 2 randomized-controlled trials evaluating the role of topical alicaforsen in ulcerative colitis (UC) failed to show short-term efficacy, patients treated with the enema formulation seemed to have a long-term benefit [19–21]. This has led to the hypothesis of a disease-modifying effect. In addition, 2 small, open label studies evaluating the role of alicaforsen in chronic pouchitis have shown promising results even in difficult-to-treat cases [22, 23].

Taken together, there might be a role for topical alicaforsen in the treatment of chronic pouchitis and left-sided UC. This case series analyzes the efficacy and safety of a 6-week course of alicaforsen as enema formulation in the treatment of left-sided UC and ulcerative proctitis.

Methods

Subjects

We performed a retrospective analysis on all patients who had received at least one dose of alicaforsen at 6 IBD referral centers in Switzerland with at least one follow-up visit (University Hospital Zurich, Triemli Hospital Zurich, Gastrozentrum Hirslanden Zurich, Tiefenauspital Bern, Kantonsspital St. Gallen, and the outpatient clinic MagenDarm AG Basel). Patient information was extracted from each patient's chart. Patients were excluded if they were under the age of 16. Diagnosis of underlying IBD had to be established based on clinical course, endoscopy and histology according to current international guidelines. As alicaforsen has currently an off-label status in Switzerland, approval from the patient's health care insurance for reimbursement and from the Swiss Agency for Therapeutic Products (SwissMedic) was needed prior to the first administration. The drug was used as retention enema, which is based on hydroypropyl-methylcellulose in a volume of 60 mL (4 mg/mL corresponding to 240 mg) and applied nightly for 6 weeks. Formulation was prepared by the manufacturer (Atlantic healthcare). For a detailed outcome analysis, only patients treated for left-sided UC and/or ulcerative proctitis were included. Patients were enrolled in the Swiss IBD Cohort Study, which an ethical approval is available for. Written informed consent had been obtained from every single patient.

Data Collection

The following data was collected from individual patient's charts: patient demographics (sex, age, smoking status), prior medical and surgical history, prior therapies and current co-medications, disease characteristics (age at disease onset, disease location disease course), laboratory parameters (full blood count, C-reactive protein, blood sedimentation rate, faecal calprotectin), endoscopic findings (if applicable) and symptom severity (stool frequency, rectal bleeding). In order to grade clinical disease activity we used the partial Mayo score and a 6-point symptom score adapted from the Mayo score [24], which both had been used in UC studies [25]. In addition, disease activity was globally assessed by the treating physician based on his interpretation of clinical, endoscopic and histological findings ranging from remission to mild, moderate, and severe activity. If applicable, total Mayo score was calculated. We further collected all data on the use of alicaforsen including exact indication, dosage, duration and side effects. In order to evaluate the efficacy of alicaforsen, we used the following definitions of clinical improvement in accordance to our prior study evaluating alicaforsen in chronic pouchitis [23]:

Presence of all of the following criteria:

– Reduction of stool frequency

– Reduction of partial Mayo score and/or 6-point symptom score

– Responsible clinician considers disease course as improvement in synopsis of clinical symptoms, quality of life and – if applicable – endoscopic findings.

The last visit within 3 months before the initiation of alicaforsen was taken as pre-treatment evaluation. Endoscopic findings were excluded if endoscopy was performed >1 year before baseline assessment. Re-assessment of disease activity had to be done within 6 months after treatment initiation. Relapse was defined as increasing clinical and/or endoscopic disease activity after a period of clinical improvement. Duration from clinical improvement (at the end of treatment) to first relapse was recorded for Kaplan-Meier analysis.

Statistical Analyses

For all statistical analyses, SPSS version 22.0.0 (2013 SPSS Science, Inc., Chicago, IL, USA) was used. Metric data is shown as medians with total range. Categorical data is summarized as the percentage of the group total. For outcome analysis (before vs. after), Wilcoxon signed rank test was used for ordinary data and for continuous variables as they showed a non-normal distribution. For calculation of the clinical improvement-to-relapse-time, a Kaplan-Meier analysis was performed. A 2-sided p value of <0.05 was regarded as statistically significant.

Results

Overview of Patients Treated with Alicaforsen

We identified 30 patients with at least one-follow-up visit, who had received at least one dose of alicaforsen. The median age was 37.5 years (17.0–69.5) when treatment with alicaforsen was initiated. Twenty-nine patients were affected by UC, while 1 patient had been diagnosed with CD. The median age at IBD diagnosis was 24.4 years (7.5–59.0). At the time of the initiation of alicaforsen, the median duration of IBD was 12.8 years (1.5–43.2). Indication for alicaforsen treatment was as follows: 12 patients were being treated for left-sided UC or proctitis, while 16 were treated for chronic pouchitis after proctocolectomy, 1 patient was treated for CD proctitis and 1 patient for ischemic pouchitis. Only in 2 patients (1 treated for CD proctitis and 1 for left-sided UC colitis), alicaforsen was discontinued early after 10 days and 5 weeks respectively. In both cases, lack of efficacy was the reason for early discontinuation. Twenty-four of the 30 patients showed an improvement of the underlying condition based on the physician's global assessment. Nineteen of those patients experienced a relapse with a median duration from improvement to relapse of 12 weeks (1–112). No adverse events were reported. Results of those patients treated for chronic refractory pouchitis have been published in a prior case series [23]. Demographic data of all patients are depicted in Table 1. Online supplementary Table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000484979) shows a synopsis of all 30 patients treated with at least one dose of alicaforsen.

Patients Treated for Left-Sided UC/Proctitis

The 12 patients treated for left-sided UC or proctitis had a median age of 36.7 years (range 17.0–69.5). Five patients were female (41.7%). The median age at UC diagnosis was 25.0 years (7.5–59.0). Median duration of UC at initiation of alicaforsen treatment was 11.8 years (1.5–14.8). Seven of the 12 patients (58.3%) had left-sided UC (Montreal Classification E2), while the remaining 5 patients (41.7%) were affected by ulcerative proctitis (Montreal Classification E1). Table 2 depicts demographic data and disease characteristics of those 12 patients treated for left-sided UC/proctitis. No history of C. difficile infection was reported, while 1 patient previously had had a CMV colitis. Four patients were prior smokers. One patient with proctitis had previously undergone left-sided hemicolectomy due to sigmoid perforation. Eleven of the 12 patients (91.7%) received a full 6-week course of 240 mg alicaforsen once daily as enema formulation, while in 1 patient, alicaforsen was discontinued early after 5 weeks due to lack of efficacy. No adverse events were reported. Indications for the use of alicaforsen were as follows: to defer systemic treatment despite a severe disease course (6/12, 50.0%), malcompliance with oral medications (1/12, 8.3%), severe course despite prior topical steroids

Table 1. Demographic data of all patients

	All patients (n = 30)
Age, years, median (range)	37.5 (17.0–69.5)
Gender, male/female, n (%)	17/13 (56.7/43.3)
Indication, n (%)	
Chronic pouchitis	16 (53.3)
Left-sided UC/proctitis	12 (40.0)
Ischaemic pouchitis	1 (3.3)
Fistulizing CD	1 (3.3)

Table 2. Demographic data and disease activity of those patients treated for left-sided UC/proctitis

	All patients with left-sided UC/ proctitis (n = 12)
Age, years, median (range)	36.7 (17.0–69.5)
Gender, male/female, n (%)	7/5 (58.3/41.7)
Age at UC diagnosis, years, median (range)	25.0 (7.5–59.0)
Duration of UC at alicaforsen treatment, years, median (range)	11.8 (1.5–14.8)
Number of daily stools, median (range)	7.0 (1.0–10.0)
Mayo score, median (range)	9.0 (4.0–11.0)
Partial Mayo score, median (range)	7.0 (1.0–8.0)
6-Point symptom score, median (range)	4.5 (0.0–5.0)
Global assessment, n (%)	
Mild	2 (16.7)
Moderate	4 (33.3)
Severe	6 (50.0)
Faecal calprotectin, μg/g, median (range)	401.0 (116.0–1,110.0)

and immunosuppressive agents (1/12, 8.3%), pregnancy with aminosalicylate (5-ASA) intolerance (1/12, 8.3%), and left sided UC before switch of anti-TNF (2/12, 16.7%). Physician's global assessment revealed a moderate-to-severe disease activity in 10 out of 12 patients (83.3%). Only 2 patients were assessed to have mild disease. No patient was in remission. At baseline, median Mayo score was 9.0 (4.0–11.0), partial Mayo score was 7.0 (1.0–8.0) and 6-point symptom score was 4.5 (0.0–5.0). Patients reported a median of 7 stools per day (1–10). For a comprehensive synopsis on each individual patient, we refer to the online supplementary Tables 2 and 3.

Overall Study Outcome

Median follow-up (time from treatment initiation to first follow-up visit) was 3.0 months (1.6–5.5 months). Six of the 12 patients were treated with alicaforsen alone, while the remaining 6 patients received concomitant therapy: 1 patient was treated with overlapping prednisone, which was tapered within the first 2 weeks, 1 patient was treated with overlapping prednisone for 2 weeks and ongoing therapy with azathioprine and 5-ASA, 1 patient was concomitantly treated with ongoing topical budesonide and 5-ASA, 1 patient continued with oral and topical 5-ASA, 1 patient continued with oral 5-ASA, azathioprine and certolizumab pegol, and 1 patient continued with infliximab. Clinical disease activity was significantly reduced at the first follow-up visit. Mean partial Mayo score and the 6-point symptom score (adapted from Mayo score) showed a decrease from 6.0 to 2.4 and from 3.7 to 1.4 respectively ($p = 0.011$ and $p = 0.008$). Total Mayo score and stool frequency both showed a considerable decrease from 8.6 to 5.3 and from 6.2 to 4.0; however differences were not statistically significant ($p = 0.092$ and $p = 0.074$). In 5 patients, no follow-up endoscopy was performed: in 2 patients because of a decrease of symptom severity and normalization of faecal calprotectin (from 1,110 to 16 and 743 to 16 μg/g, respectively), in 1 patient because of the complete absence of clinical symptoms (partial Mayo score 0), in 1 patient due to the very short period of clinical improvement (1 week) and in 1 patient due to loss of follow-up after clinical re-assessment showing clinical improvement (partial Mayo score pre 4 vs. post 2). Faecal calprotectin as a marker of intestinal disease activity was considerably reduced after alicaforsen treatment (mean 484.4 vs. 179.5 μg/g); however, the difference did not reach statistical significance ($p = 0.063$), as a complete set (both pre- and post-treatment) was available only for 7 of the 12 patients. For subgroup analysis, we excluded patients with mild disease at treatment initiation – as those are less likely to benefit from alicaforsen. This moderate-severe disease subgroup ($n = 10$) showed the following pre vs. post-treatment changes: Mayo score 9.5 vs. 6.8 ($p = 0.197$), partial Mayo score 6.8 vs. 2.9 ($p = 0.020$), 6-point symptom score 4.2 vs. 1.7 ($p = 0.013$), stool frequency 7.15 vs. 4.6 stools/day ($p = 0.110$) and faecal calprotectin 554.8 μg/g vs. 208.0 ($p = 0.075$).

Clinical improvement was achieved in 10 out of the 12 patients (83.3%). Median duration of clinical improvement (at the end of treatment) was 18.0 weeks (1.0–112.0). In 7 of the 10 patients with clinical improvement, a relapse was observed (70%). Median time from improvement (at the end of treatment) to relapse was 6 weeks (1.0–112.0). Three patients showed a sustained clinical improvement; in those patients, the duration of clinical improvement was 36, 69, and 73 weeks respectively (Fig. 1a–d, 2).

Discussion

This retrospective case series analyzes the efficacy and safety of alicaforsen as enema formulation in the treatment of left-sided UC and ulcerative proctitis in 12 patients in Switzerland. After a median of 3 months, patients treated with a 6-week course of alicaforsen showed a significant reduction in clinical disease activity (as assessed by partial Mayo score and 6-point symptom score). We found that 10 out of 12 patients showed a clinical improvement on being given alicaforsen; however, in 7 of these patients (70%), a relapse occurred. Median duration of clinical improvement was 18.0 weeks. In 3 patients with a sustained response, the duration of clinical improvement was more than 9 months.

Data on the potential role of alicaforsen in IBD treatment is inconsistent. In CD, randomized-controlled trials with intravenous/subcutaneous drug formulation failed to show short-term efficacy of alicaforsen (at weeks 12 and 14, respectively), although post-hoc analysis suggested higher response rates with higher drug concentrations [16–18, 26]. In left-sided UC, in a small open label study, Miner at al. [27] could demonstrate that alicaforsen enema provides local treatment without meaningful systemic exposure; at week 6, disease activity index was reduced by 46% with 12 out of 15 patients having achieved clinical improvement. Two larger randomized, controlled trials by van Deventer et al. [19] failed to show (short-term) efficacy of the enema formulation: disease activity at week 6 was not significantly reduced compared to placebo and mesalazine respectively [20]. Nonetheless, a prolonged clinical response was observed in both trials with a significant reduction in dis-

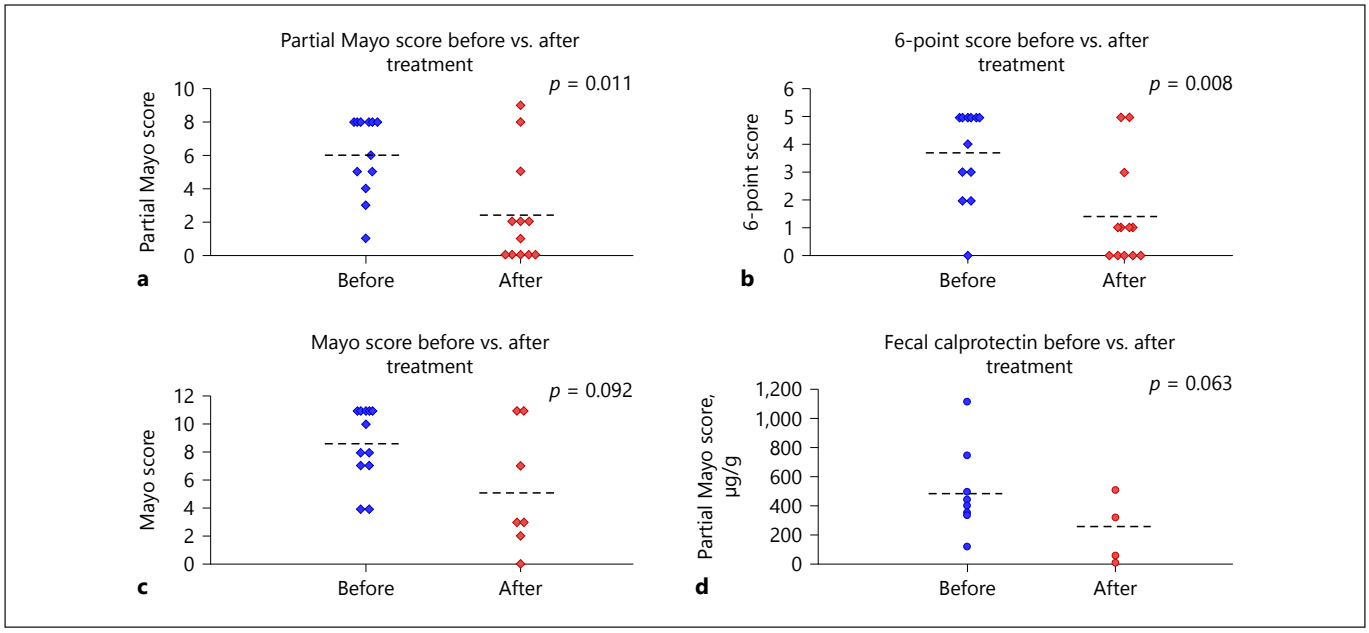

Fig. 1. a–d Clinical disease activity (partial Mayo score [**a**], 6-point symptom scale [**b**], Mayo score [**c**] and faecal calprotectin [**d**]) at baseline versus at first follow-up visit after treatment.

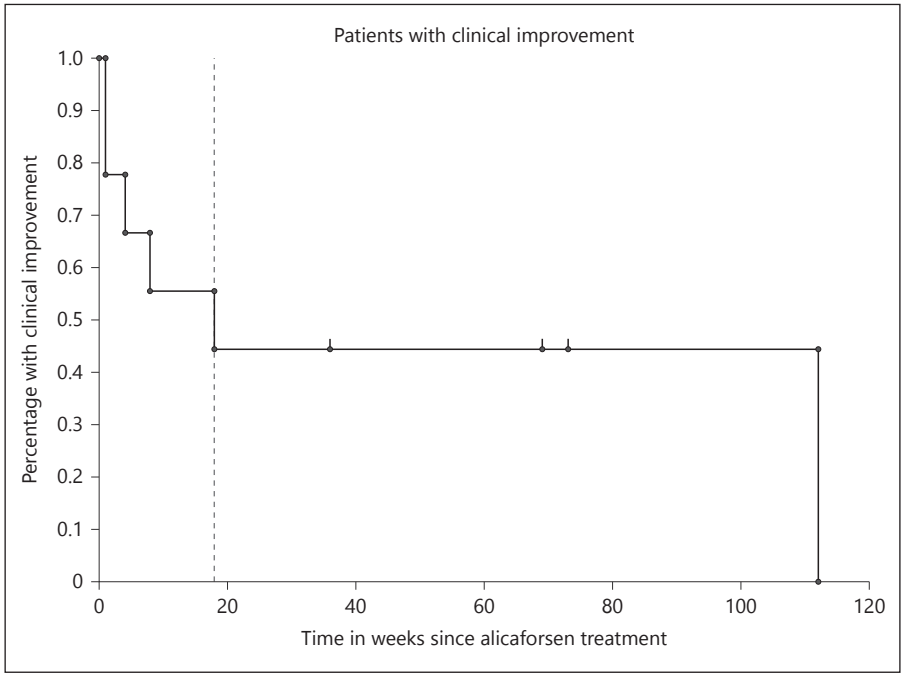

Fig. 2. Kaplan-Meier analysis of duration of clinical improvement.

ease activity at weeks 18 and 30 compared to placebo (51 vs. 18% and 50 vs. 11%) and a significant longer duration of response compared to mesalazine (146 vs. 54 days). In a smaller randomized controlled trial, van Deventer et al. [28] showed both a short-term and long-term benefit from alicaforsen enema treatment: disease activity was reduced by 78% at day 29 and by 68% at 3 month compared to a placebo response of 28 and 11.5% respectively. Given the fact that the half-life period of alicaforsen is only 24 h, these findings have led to the concept of a disease-modifying ef-

fect. A durable effect may be achieved by modification of immunological factors that permit continuous colonic mucosal inflammation in UC [20].

Our results with a clear and fast reduction of clinical disease activity (Mayo score –27%, partial Mayo score –60%, and 6-point symptom score –62%) are consistent with those of the open label study by Miner et al. [27] and the small randomized-controlled trial by van Deventer [28]. The clinical improvement rate of 83.3% (10 out of 12) is comparable to that of Miner et al. [27] (clinical improvement in 12/15 patients [80%]). These findings highlight the potential short-term benefit from a single 6-week course of alicaforsen. However, 7 of the 10 patients with initial clinical improvement had a clinical relapse. The median duration of clinical improvement of 18.0 weeks (corresponding to 126 days) is nearly as high as indicated by Miner et al. [20] (146 days). Four patients had a clinical improvement of more than 9 months, 3 of them without any further IBD treatment, the remaining patient with ongoing topical and oral 5-ASA only. Four patients had a clinical improvement of less than or equal to 8 weeks. It remains to be determined, who among the patients show a prolonged response after a single 6-week course of alicaforsen and who do not. Repeated treatment courses and/or maintenance therapy may lead to longer response rates as it has been reported in the case series regarding alicaforsen in the treatment of chronic pouchitis [23]. So far, none of our patients had received a second trial due to alicaforsen's status as unlicensed medicine and the difficulty of reimbursement by the Swiss health insurances.

No serious adverse events were reported underlying the safety of the topical applied drug. In addition, topical delivery was well tolerated and none of the patients showed malcompliance. This is especially noteworthy, as patients and physicians appear to be somewhat reluctant to administer topical treatment options in UC in real-life [29].

A limitation of our case series certainly is its retrospective nature and subsequently the lack of controls and blinding. Six patients (50%) received concomitant treatment. However, 4 of the 6 patients only continued the medications, which they had been on for a long time. In 2 patients, oral prednisone was tapered. The tapering of the steroids was well tolerated under alicaforsen treatment. The 2 patients with prior and ongoing anti-TNF exposure did show the worst outcome (1 patient with no improvement, 1 patient with a relapse after 1 week). The concern that anti-TNF co-medication may have affected the study outcome positively seems to be negligible. In contrast, failure to respond to anti-TNF may be a negative predictor for treatment success with alicaforsen. The presented results are based on the partial Mayo score and the 6-point symptom score (adapted from the Mayo score). Full Mayo score was applied only in 7 of the 12 patients due to the lack of follow-up endoscopies. However, both the partial score and the symptom score have been previously validated for UC [25]. The study population was limited due to the drug's status as unlicensed medicine and difficulty in reimbursement of the study drug from health care insurances. However, the study sample was nearly equal to that of the open label study by Miner et al. [27].

In conclusion, a 6-week course of alicaforsen was safe and efficacious in inducing clinical improvement in left-sided UC and proctitis, and is – at least in some patients – sufficient for maintaining clinical improvement. Further studies with more patients are needed to answer the following questions: Who among patients may benefit from a single 6-week course? Who may need repeated treatment courses?

Disclosure Statement

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Off-Label Use

Alicaforsen has been granted the orphan drug designation and is currently prescribed as an unlicensed medicine.

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